

CLAIMS

1. Method for identifying compounds capable of modulating adipocyte differentiation, wherein (i) a test compound is contacted with a population of genetically modified pre-adipocyte cells, comprising a recombinant nucleic acid coding a *REV-ERB ALPHA* receptor, (ii) adipocyte differentiation of said cells is measured or determined and (iii) preferably, said differentiation is compared with adipocyte differentiation of said same pre-adipocyte cells in the absence of said test compound.

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2. Method according to claim 1, wherein the test compound is contacted with cells overexpressing the *REV-ERB ALPHA* receptor in the presence of at least one activator of a receptor involved in the adipocyte differentiation process.

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3. Method according to claim 2, wherein the activator of the receptor involved in the adipocyte differentiation process is an activator of the PPAR GAMMA receptor.

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4. Method according to claim 3, wherein the activator of the receptor involved in the adipocyte differentiation process is selected in the group consisting of in particular : thiazolidinediones, such as rosiglitazone, troglitazone, englitazone, ciglitazone, pioglitazone, or KRP-297, N-(2-benzoylphenyl)-L-tyrosines and 15-deoxy-delta 12,14-prostaglandin J2.

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5. Method according to claim 1, wherein the test compound is contacted with genetically modified pre-adipocyte cells in the presence of at least one activator of a gene involved in the adipocyte differentiation process.

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6. Method according to claim 5, wherein the activator of a gene involved in the adipocyte differentiation process is an activator of the PPAR gamma gene.
7. Method according to claim 6, wherein the activator of the PPAR gamma gene is selected in the group comprising C/EBP beta, C/EBP delta and ADD1 (SREBP1c).

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8. Method according to any one of claims 1 to 7, wherein the *REV-ERB ALPHA* receptor comprises sequence SEQ ID NO : 4 or a fragment or functional variant thereof.
9. Method according to any one of claims 1 to 8, wherein the recombinant nucleic acid comprises sequence SEQ ID NO : 3 or a fragment thereof
10. Method according to any one of claims 1 to 9, wherein the recombinant nucleic acid additionally comprises sequence SEQ ID NO : 1 or a fragment thereof comprising sequence SEQ ID NO : 2.
11. Method according to any one of claims 1 to 10, wherein the recombinant nucleic acid is incorporated in a plasmid vector.
12. Method according to any one of claims 1 to 10, wherein the recombinant nucleic acid is incorporated in a viral vector.
13. Method according to any one of claims 1 to 12, wherein the recombinant nucleic acid is integrated in the cellular genome.
14. Method according to any one of claims 1 to 13, wherein adipocyte differentiation is measured (i) by staining the differentiated cells, preferably with a stain selected in the group consisting of Oil Red O and Sudan Black, (ii) by determining fatty acid transport or synthesis, and/or (iii) by determining the expression of at least one marker specific of differentiated adipocytes, preferably a marker selected in the group consisting of aP2, adipsin and leptin.
15. Method for identifying compounds capable of modulating adipocyte differentiation, wherein it comprises (i) contacting a test compound and a nucleic acid comprising sequence SEQ ID NO : 1, preferably SEQ ID NO : 2, or a functional equivalent thereof, in the presence of the PPAR GAMMA receptor, (ii) verifying a binding of the PPAR GAMMA receptor to said nucleic acid and, optionally, (iii) comparing said binding with that observed in the absence of test compound, the test compounds modulating said

binding of the PPAR GAMMA receptor being compounds modulating adipocyte differentiation.

16. Method for identifying compounds capable of modulating adipocyte differentiation,
5 wherein it comprises contacting a test compound and the PPAR GAMMA receptor with a reporter system comprising (i) a transcriptional promoter comprising one or more copies of sequence SEQ ID NO : 1, preferably of sequence SEQ ID NO : 2, or a functional variant thereof and (ii) a reporter gene, and evaluating the activity of the test compound by measuring its effect on expression of the reporter gene induced by the PPAR GAMMA
10 receptor.

17. Use of a compound identified by a method according to any one of claims 1 to 16, or of an analog thereof, for preparing a medicament for the preventive or curative treatment of a metabolic disease.

18. Use of a compound identified by a method according to any one of claims 1 to 16, or of an analog thereof, for preparing a medicament for the preventive or curative treatment of diabetes, obesity, insulin-resistance or syndrome X.

19. Genetically modified pre-adipocyte cell, wherein it comprises a recombinant nucleic acid coding a *REV-ERB ALPHA* receptor, said recombinant nucleic acid additionally comprising sequence SEQ ID NO : 1 or a fragment thereof comprising sequence SEQ ID NO : 2.

20. Cell according to claim 19, wherein the *REV-ERB ALPHA* receptor comprises sequence SEQ ID NO : 4 or a fragment or functional variant thereof.

21. Cell according to claim 19 or 20, wherein the recombinant nucleic acid comprises sequence SEQ ID NO : 3 or a fragment thereof.

22. Cell according to any one of claims 19 to 21, wherein the recombinant nucleic acid is incorporated in a plasmid vector.

23. Cell according to any one of claims 19 to 21, wherein the recombinant nucleic acid is incorporated in a viral vector.
24. Cell according to any one of claims 19 to 23, wherein the recombinant nucleic acid is
5 integrated in the cellular genome.
25. Genetically modified pre-adipocyte cell, wherein it comprises a recombinant nucleic acid coding a *REV-ERB ALPHA* receptor, the recombinant nucleic acid being incorporated in a viral vector.
- 10 26. Genetically modified pre-adipocyte cell, wherein it comprises a recombinant nucleic acid coding a *REV-ERB ALPHA* receptor, the recombinant nucleic acid being integrated in the cellular genome.
- 15 27. Cell according to claim 25 or 26, wherein the *REV-ERB ALPHA* receptor comprises sequence SEQ ID NO : 4 or a fragment or functional variant thereof.
28. Cell according to any one of claims 25 to 27, wherein the recombinant nucleic acid comprises sequence SEQ ID NO : 3 or a fragment thereof.
- 20 29. Cell according to any one of claims 25 to 28, wherein the recombinant nucleic acid additionally comprises sequence SEQ ID NO : 1 or a fragment thereof comprising sequence SEQ ID NO : 2.
- 25 30. Method for preparing a pre-adipocyte cell according to any one of claims 19 to 29, wherein a recombinant nucleic acid coding a REV ERB ALPHA receptor is introduced into a pre-adipocyte cell.
- 30 31. Method according to claim 30, wherein the pre-adipocyte cells are selected from among the cell lines 3T3-L1, 3T3-F442A, ob17 and ob1771.
32. Method according to any one of claims 30 or 31, wherein the nucleic acid is introduced by transfection with a plasmid vector.

33. Method according to claim 32, wherein it comprises cotransfecting the cells with a plasmid vector comprising said recombinant nucleic acid and a plasmid vector comprising an antibiotic resistance gene, and wherein the cells are selected for their resistance to said antibiotic and for their expression of said recombinant nucleic acid.
34. Method according to claim 32, wherein the nucleic acid is introduced by transfection with a plasmid vector additionally comprising an antibiotic resistance gene, and wherein the cells are selected for their resistance to said antibiotic and for their expression of said recombinant nucleic acid.
35. Method according to claim 32, wherein the nucleic acid is introduced by transfection with a plasmid vector additionally comprising an antibiotic resistance gene and a eukaryotic origin of replication, and wherein the cells are selected for their resistance to said antibiotic and for their expression of said recombinant nucleic acid.
36. Method according to any one of claims 30 or 31, wherein the nucleic acid is introduced by infection with a viral vector.
37. Method according to claim 36, wherein the infection is realized by means of a recombinant adenocirus or retrovirus.
38. Method according to any one of claims 30 to 37, wherein the recombinant nucleic acid comprises SEQ ID No : 3 or a fragment thereof.
39. Method according to any one of claims 30 to 38, wherein the recombinant nucleic acid additionally comprises one or more transcriptional regulatory regions, typically a transcriptional promoter and/or terminator.
40. Method according to claim 39, wherein the recombinant nucleic acid comprises sequence SEQ ID NO : 1 or a fragment thereof comprising sequence SEQ ID NO : 2.



41. Method according to any one of claims 30 to 40, wherein, after infection or transfection, stable pre-adipocyte cell lines in culture are selected.
42. Defective recombinant virus, preferably a defective recombinant adenovirus or retrovirus, wherein it comprises in its genome a nucleic acid coding a *REV-ERB ALPHA* receptor.